

Remarks

I. Status of the Claims

Reconsideration of this Application is respectfully requested.

Claims 63, 68-76, 78-88, 94, 97-116, 118-123, 126 and 128-139 are pending in the application, with claim 63 being the sole independent claim. Claims 74, 99, 105-107, and 111-113 are withdrawn from consideration, but remain pending. Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

II. Summary of the Office Action

In the Office Action dated October 15, 2009, the Examiner has made three rejections of the claims. Applicants respectfully offer the following remarks concerning each of these elements of the Office Action.

III. The Rejection Under 35 U.S.C. § 103(a) Is Traversed

In the Office Action at page 2, the Examiner maintained the rejection of claims 63, 68-73, 75, 76, 78-88, 94, 97, 98, 100-104, 108-110, 114-116, 118-120, 124, 126, 128-132 and 134-139 under 35 U.S.C. § 103(a) as being unpatentable over Stockley *et al.* (U.S. Patent No. 6,159,728; hereinafter "Stockley") in view of Deghenghi *et al.* (U.S. Patent Publ. No. 2002/0187938 A1; hereinafter "Deghenghi"), Kojima *et al.* (*Nature* 402: 656-660 (1999); hereinafter "Kojima") and Maita *et al.* (Gen Pept Accession VCBPQB, 1971; hereinafter "Maita"), and

further in view of Nielsen *et al.* (U.S. Patent No. 6,548,651; hereinafter "Nielsen"). Applicants respectfully traverse this rejection.

The presently claimed invention provides for compositions which are able to induce high levels of antibodies that recognize, surprisingly, the n-octanoylated form of ghrelin as shown in the present specification, in particular in Example 17. Furthermore, generated antibodies also recognized the alternative isorform, Ghrelin-desQ14. As a result, antibodies generated from vaccination with C- or N-terminally linked ghrelin and ghrelin peptide, respectively, to a core particle or, preferably to a VLP, were able to block the entry of n-octanoylated ghrelin into the brain and modulated food intake in mice. Thus, the presently claimed invention focuses on vaccination strategies against active ghrelin as a treatment for obesity and other related diseases (*see, e.g.*, published application at Page 6, l. 3-11 of PCT).

In contrast, the references cited by the Examiner, viewed alone or in combination, neither disclose nor suggest all of the elements of the present claims in their proper association and function, with any degree of predictability and expectation of success. Thus, the Examiner has not satisfied the burden of establishing a *prima facie* case of obviousness based upon the cited art. *See In re Piasecki*, 745 F.2d 1468, 1471-72 (Fed. Cir. 1984).

The factors to be considered in making an obviousness rejection under 35 U.S.C. § 103(a) are: (a) the scope and content of the prior art; (b) the differences between the prior art and the claims at issue; and (c) the level of ordinary skill in the pertinent art. *See Graham v. John Deere*, 86 S.Ct. 684

(1966), and MPEP §2141. This analysis has been the standard for 40 years, and remains the law today. *See KSR International Co v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). The critical role of the Office personnel as fact finders when resolving *Graham* inquiries has been emphasized by the Office within its published Examination Guidelines. *See* "Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in *KSR International v. Teleflex Inc.*", *Fed. Reg.* 72:57526- 57535 (October 10, 2007), hereinafter "Examination Guidelines." Establishment of a *prima facie* case of obviousness requires that the Examiner factually show that the references in combination disclose all of the elements of the claims in their proper function(s), as well as provide a reasoned articulation that the combination of elements would have been known to produce a predictable result. In the present case, this burden has not been met.

Applicants note that the cited references do not disclose or suggest a composition comprising a virus-like particle with at least one first attachment site *wherein said first attachment site is a lysine residue of said virus-like particle and said second attachment site is a cysteine residue*, as recited in the present claims. In particular, Stockley does *not* disclose the association of non-peptide covalent bonds of *lysine residues of virus-like particles of an RNA-bacteriophage* as first attachment sites with *cysteine residues of the ghrelin antigens* as second attachment sites forming highly ordered and repetitive ghrelin arrays representing for the induction of immune responses against ghrelin. Indeed, the Examiner has already conceded this point in the prior Office Action by withdrawing the

obviousness rejection of the same claims over Stockley as the primary reference in view of Deghengi, Kojima and Maita. *See* Office Action dated February 4, 2009, at page 4, third paragraph. Accordingly, Stockley is seriously deficient as a primary reference upon which to attempt to base a *prima facie* case of obviousness, and these deficiencies are clearly not filled (as the Examiner has conceded) by the disclosures of Deghengi, Kojima and Maita.

In an attempt to fill the deficiencies in the disclosures of Stockley, Deghengi, Kojima and Maita in the prior Office Action, however, the Examiner cited a *fifth* reference -- Nielsen -- to allegedly provide the disclosure that is missing from the other four references used in making this rejection. In citing Nielsen in the prior Office Action, as an additional reference seeking to fill the deficiencies in Stockley, Deghengi, Kojima and Maita, the Examiner stated that:

Nielsen et al. teach a non-peptide heterobifunctional cross-linker succinimidyl 6-CPmaleimido-propionamido) hexanoate (SMPH) covalently linking peptides with nucleic acid molecules representing bacterial antigens through either a cysteine (C) or a lysine (K) residue (see claim 1, Tables 1 and 4, column 8, lines 17-41 and column 9, lines 4-10).

* * * * *

Nielsen teaches that the SMPH is a suitable linker for attachment of peptides with nucleic acids (see claim 1, Tables 1 and 4, column 8, lines 17-41 and column 9, lines 4-10).

Office Action of February 4, 2009, at page 3, lines 15-18, and at page 4, lines 2-3.

These remarks are repeated by the Examiner in the present Office Action on page 5, making it clear that the Examiner considers Nielsen to be the "missing

piece" that completes the multi-part puzzle that the Examiner attempts to construct by pulling together disparate pieces of disclosure from multiple references in an attempt to render obvious the presently claimed invention. However, Applicants respectfully submit that the subject matter relating to the specific non-peptide covalent linkage of virus-like particles of an RNA-bacteriophage and ghrelin or ghrelin peptides by way of first attachment sites being lysine residues of virus-like particles of an RNA-bacteriophage and second attachment sites being cysteine residues of ghrelin or ghrelin peptides, and thus the construction of the presently claimed compositions, is knowledge which simply is *not* disclosed in any of the cited references, including Nielsen. In fact, far from disclosing such compositions, these references at best provide nothing more than a collection of *some* of the parts of the presently claimed compositions, without providing any guidance whatsoever as to how such parts should or could be assembled so as to make and use the presently claimed compositions.

Instead, the Examiner appears to be relying upon the present specification to provide the guidance that is missing from the cited references. However, using the present specification in this way -- as a blueprint to assemble the presently claimed compositions from an assortment of pieces that may be at best distributed in a collection of multiple unrelated references -- is the very epitome of hindsight reconstruction. As the Federal Circuit has held numerous times, such a hindsight analysis is impermissible -- instead, the Examiner must show suggestions, explicit or otherwise, that would have compelled one of ordinary skill to combine the cited references in order to make and use the claimed invention. *See, e.g.,*

Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1143 (Fed. Cir. 1985)

(“When prior art references require selective combination by the [fact-finder] to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself.”); *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) (“One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.”); *In re Pleuddemann*, 910 F.2d 823, 828 (Fed. Cir. 1990) (noting that use of an applicant’s specification as though it were prior art to support an obviousness determination is legal error); *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991) (holding that both the suggestion to combine references, and a reasonable expectation of success in making the claimed invention, “must be founded in the prior art, not in the applicant’s disclosure.”). The Board has also provided the same mandate on this issue:

[I]t is impermissible to use the claimed invention as an instruction manual or “template” to piece together isolated disclosures and teachings of the prior art so that the claimed invention may be rendered obvious a rejection based on § 103 must rest on a factual basis, with the facts being interpreted without hindsight reconstruction of the invention from the prior art. In making this evaluation, the examiner has the initial duty of supplying the factual basis for the rejection he advances. He may not, because he doubts that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in the factual basis.

Ex parte Haymond, 41 USPQ2d 1217, 1220 (Bd. Pat. App. Int. 1996). Thus, the use of hindsight analysis in the present case is impermissible and cannot be the basis of an attempt to establish a *prima facie* case of obviousness.

In addition, there is no basis for concluding that an invention would have been obvious solely because it is a combination of elements that were known in the art at the time the invention was made. *See Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 (Fed. Cir. 1995). Instead, what is needed is a reason or suggestion in the prior art that would have led one of ordinary skill to combine the cited references, and that would also have suggested a reasonable likelihood of success in making or using the claimed invention as a result of that combination. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). These standards are not met in the present Office Action, since all the Examiner has done is point out a combination of elements that are allegedly disclosed in the cited references, without articulating a sound reason for one of ordinary skill to have combined those elements in such a way as to have had a reasonable expectation of success in making or using the presently claimed invention. There is absolutely nothing in Stockley, Nielsen or any of the other cited references that would have led one of ordinary skill in the art to have used a *lysine residue of a virus-like particle of an RNA-bacteriophage* as a first attachment site, and to bind such a residue via a non-peptide covalent bond to a *cysteine residue of ghrelin or a ghrelin peptide* as a second attachment site, thereby forming a highly ordered and repetitive ghrelin array useful for the induction of immune responses against ghrelin. Moreover, the Examiner has pointed to no acceptable objective evidence or sound scientific reasoning that would have led one of ordinary skill to have made such a change to the disclosure of Stockley, even in view of Nielsen or any of the other references. Instead, in stating three separate times, without any support whatsoever, that such

a combination of the disclosures of the cited references “would have yielded predictable results to one of ordinary skill in the art” (*see* Office Action at page 6, first and second paragraphs, and page 7, first paragraph), the Examiner appears to assume that the reason for making such a change to the disclosure of Stockley, and that such a change “would have yielded predictable results,” exists in the “general knowledge” in the art. Importantly, however, the Examiner has provided absolutely no basis in logic or sound scientific reasoning to support such an assumption, other than to state that the various pieces of the presently claimed compositions are disclosed in the cited references. As discussed above, the requisite reason for making a change to the disclosure(s) of the cited reference(s) must be found either in the prior art or in knowledge that is generally available to those of ordinary skill in the art; a baseless assumption of such knowledge is legally impermissible. *See In re Fine*, 5 USPQ2d at 1600; *see also See In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313 (Fed. Cir. 2000). Moreover, as the Federal Circuit has held:

[t]he range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not “evidence.”

In re Dembiczak, 175 F.3d 994, 999 (Fed. Cir. 1999) (citations omitted). Since the Examiner has provided no actual evidence to support the conclusory statements that Stockley and Nielsen and the remaining references in combination render the present invention obvious, and that the reason for combining their disclosures is because such a combination “would have yielded predictable

results,” Applicants respectfully assert that a *prima facie* case of obviousness has not been established.

The Federal Circuit has also held that in unpredictable arts such as chemicals and biotechnology, the Supreme Court’s *KSR* opinion assumes, for establishing a finding of obviousness: (1) a starting reference point or points in the art; (2) reasons for one skilled in the art to make modifications to the prior art compound(s); and (3) reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions." *Eisai Co. v. Dr. Reddy’s Laboratories, Ltd.*, 533 F.3d 1353 (Fed. Cir. 2008). In making the present rejection, the Examiner has apparently used Stockley as a starting reference point in the art, but then has not provided a sound reason for one of ordinary skill to have made a modification to the attachment site(s) disclosed in Stockley, and particularly to have narrowed the possible modifications to a finite number of identified, predictable solutions, so as to arrive at the presently claimed invention in which the first attachment site is a lysine residue of an RNA bacteriophage VLP and the second attachment site is a cysteine residue of ghrelin or a ghrelin peptide, instead the constructs disclosed in Stockley. Simply contending, as the Examiner has done, that combining all of the pieces plucked indiscriminately out of five separate references “would have yielded predictable results to one of ordinary skill in the art,” does not meet the *Eisai* requirements for articulation of a reason to specifically select a lysine residue of an RNA bacteriophage VLP as a first attachment site, and a cysteine residue of ghrelin or a ghrelin peptide as a second attachment site, from all of the other possible modifications that could

have been made to the Stockley compositions even in view of the other references, including Nielsen. Moreover, the Examiner's unsupported contention does not provide a reason to even have *made* such modifications to Stockley, whether in view of Nielsen or any of the other references. As a result, the requirements for obviousness under *KSR* as interpreted by the Federal Circuit in *Eisai* have not been met, and a *prima facie* case of obviousness therefore has not been established.

Therefore, none of Deghengi, Kojima, Maita and Nielsen supplements the deficiencies of Stockley discussed in detail above, and the references cannot be properly combined in an attempt to make out a *prima facie* case of obviousness of the formerly pending and present claims. Hence, Applicants respectfully assert that the present claims would not have been obvious over the cited references.

In view of the foregoing remarks, Applicants respectfully assert that the claims as currently presented would not have been obvious over any of the cited references, alone or in combination, and particularly without the need for resorting to impermissible hindsight reconstruction using Applicants' own disclosure as guidance. Thus, a *prima facie* case of obviousness of the present claims has not been made, and cannot be made using the cited references. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) over these reference are respectfully requested.

IV. The Double-Patenting Rejection Over the '350 Application Is Traversed

In the Office Action at pages 7-8, the Examiner has provisionally rejected claims 63, 68-73, 75, 76, 78-88, 94, 97, 98, 100-104, 108-110, 114-116, 118-120, 124, 126, 128-132 and 134-139 on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-23 of commonly owned, co-pending U.S. Appl. No. 11/663, 350 ("the '350 application"). Applicants respectfully traverse this rejection.

The priority date of the '350 application is September 21, 2005, whereas the priority date of the present application is July 18, 2003. Applicants thus note that the priority date of the '350 reference application used in making this obviousness-type double patenting rejection is *after* the priority date of the present application. Hence, the present application is "the earlier filed application of the two pending applications" as that phrase is meant in MPEP § 1490.V.D. Applicants believe that the amendments and arguments presented herein will place the present application into condition for allowance except for the obviousness-type double patenting rejections. Thus, Applicants respectfully request that the Examiner hold this rejection in abeyance until the arguments and amendments herewith have been considered, and to withdraw this rejection upon allowance of the present claims in accordance with MPEP § 1490.V.D.

V. The Double-Patenting Rejection Over the '716 Application Is Traversed

In the Office Action at page 8, the Examiner has provisionally rejected claims 63, 68-73, 75, 76, 78-88, 94, 97, 98, 100-104, 108-110, 114-116, 118-120, 124, 126, 128-132 and 134-139 on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 2, 4, 8, 13-23, 25 and 36-51 of commonly owned, co-pending U.S. Appl. No. 11/664,716 ("the '716 application"). Applicants respectfully traverse this rejection.

The priority date of the '716 application is October 5, 2005, whereas the priority date of the present application is July 18, 2003. Applicants thus note that the priority date of the '716 reference application used in making this obviousness-type double patenting rejection is *after* the priority date of the present application. Hence, the present application is "the earlier filed application of the two pending applications" as that phrase is meant in MPEP § 1490.V.D. Applicants believe that the amendments and arguments presented herein will place the present application in condition for allowance except for the obviousness-type double patenting rejections. Thus, Applicants respectfully request that the Examiner hold this rejection in abeyance until the arguments and amendments herewith have been considered, and to withdraw this rejection upon allowance of the present claims in accordance with MPEP § 1490.V.D.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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